REMARKS

Claims 1-3, 5-10, 12-40, and new claims 41-42 are pending in this application for the Examiner's review and consideration. Claims 4 and 11 were canceled without prejudice. Claim 1 was amended to delete the feature that the diluent, binder, disintegrant, and lubricant are not the same and to recite that the solid pharmaceutical composition is free of lactose (*See e.g.,* Specification, page 5, line 30; page 8, lines 14-20; and original claim 2) and is in the form of a tablet (*See e.g.,* Specification, page 37, lines 17-23, Examples 4 and 8; and original claim 4). Claim 2 was amended to recite that the composition comprises a diluent, a binder, a disintegrant, and a lubricant (*See, e.g.,* original claim1). Claim 3 was amended to depend from claim 2. Claim 9 was amended to recite that the solid pharmaceutical composition is free of lactose (*See e.g.,* Specification, page 5, line 30; page 8, lines 14-20; and original claim 2) and is in the form of a tablet (*See e.g.,* Specification, page 37, lines 17-23, Examples 4 and 8; and original claim 11). Claim 16 was amended to more clearly recite that the norastemizole particles are individually coated (*See, e.g.,* Specification, page 17, lines 14-20). Claim 22 was amended to depend from claim 2. New claim 41 depends from claim 1 and recites that the diluent, binder, disintegrant, and lubricant are not the same (*See, e.g.,* original claim 1). New claim 42 depends from claim 16 and recites that the norastemizole is present in an amount of from about 1 mg to 200 mg [(*See e.g.,* Specification, page 19, lines 19-21). No new matter has been added by these new claims so that their entry at this time is warranted.

The Invention

The currently pending claims are directed to novel solid pharmaceutical compositions for the treatment of histamine-induced disorders. The compositions comprise norastemizole, or a pharmaceutically acceptable salt thereof, and are free of lactose and in the form of a tablet (claims 1-3, 5-10, 12-15, 22-24, and 41-42) or comprise coated particles of norastemizole, or a pharmaceutically acceptable salt thereof (claims 16-21). The claimed compositions have improved thermal and chemical stability even in the presence of excipients that are incompatible with norastemizole, such as lactose and other mono- and di-saccharides (*See, e.g.,* Specification, page 9, lines 14-37). The present invention is also directed to methods of treating an allergic disorder in a mammal which comprises administering the norastemizole compositions of the invention (claims 25-40).

The Rejection of Claims 1-6 and 25-28 Under 35 U.S.C. § 103a)

Claims 1-6 and 25-28 were rejected under 35 U.S.C § 103(a) as being obvious over international published application WO 94/07495 to Woosley ("Woosley") for the reasons set forth on pages 2-3 of the Office Action. Applicants respectfully traverse.

Woosley discloses pharmaceutical compositions comprising norastemizole and methods of treating allergic disorders and other disorders with norastemizole.

The Examiner alleges that Woosley teaches pharmaceutical compositions comprising norastemizole with and without lactose. Applicants respectfully submit that Woosley merely discloses the use of norastemizole for the treatment of allergic disorders as well as various conventional preparations and dosage forms of norastemizole (*See, e.g.*, Woosley at page 10, line 24 to page 11, line 32) but does not disclose or suggest a pharmaceutically acceptable lactose-free norastemizole compositions in the form of a *tablet*, much less one having improved stability.

The Examiner notes that that Woosley discloses a lactose free composition in Example 4. The composition disclosed in Example 4, however, is a capsule and not a tablet. The mere disclosure in Woosley of a capsule that is free of lactose does not disclose or suggest formulating a norastemizole containing *tablet* that is lactose free. There is absolutely no disclosure or suggestion in Woosley of a lactose free norastemizole composition in the form of a tablet. Applicants have discovered that lactose, a common excipient used to formulate tablets (*See e.g.,* Specification, page 3, lines 12-20) is incompatible with norastemizole (*See e.g.,* Specification, page 10, lines 10-30). Woosley fails to disclose or suggest the incompatibility of norastemizole with lactose. There is simply no recognition in Woosley of the incompatibility of norastemizole with lactose. Indeed, Woosley, discloses norastemizole preparations containing lactose (*see, e.g.*, Woosley, Example 5) and sugars (*see, e.g.*, Woosley at page 10, lines 24-31). In fact, Example 5 of Woosley, the only example of a tablet, includes lactose in the formulation. The mere disclosure in Woosley of a single lactose free composition in the form of a capsule would not motivate one of ordinary skill in the art to formulate a lactose-free norastemizole composition in the form of a tablet, as presently claimed.

Further, Woolsey does not provide a reasonable expectation of success in formulating lactose-free composition in the form of a tablet. Indeed, as noted above, lactose is a common ingredient used to formulate tablets and Woosley says nothing about the incompatability of norastemizole and lactose. Accordingly, Woosley does not render claims 1-6 and 25-28 obvious. For the above reasons, Applicants respectfully request that the rejection of claims 1-6 and 25-28 be reconsidered and withdrawn.

The Rejection of Claim 2 Under 35 U.S.C. § 103a)

Claim 2 was rejected under 35 U.S.C. § 103(a) as being obvious over Woosley in view of S.M. Blaug *et al.*, *J. Pharm. Sci.*, 61(11):1770-1775 (1972) ("Blaug") and R. Castello *et al.*, *J. Pharm. Sci.*, 51(2):106-108 (1962) ("Castello") for the reasons set forth on pages 3-4 of the Office Action. Since Applicants have amended claim 1 to include the features of claim 2, Applicants will address the rejection with respect to claim 1, as amended. Applicants respectfully traverse the rejection for the reasons set forth below.

Castello *et al.* tested the compatibility of amphetamine sulfate (a primary amine salt) with lactose and found that a mixture of lactose and amphetamine sulfate discolored, especially in the presence of alkaline lubricants such as magnesium stearate.

Blaug *et al.* tested dextroamphetamine sulfate (a primary amine salt) with spray-dried lactose and found that the lactose formed a Schiff base (*i.e.*, an imine) in the presence of dextroamphetamine sulfate.

Claims 1, as amended, recites a lactose-free pharmaceutical composition comprising norastemizole (a secondary amine). This composition is not rendered obvious by Woosley, alone or in combination with Blaug and Castello. As discussed above, Woosley does not disclose or suggest a lactose free norastemizole composition in the form of a tablet or recognize the incompatibility of norastemizole and lactose-based excipients. Blaug and Castello do not remedy the deficiencies of Woosley. Blaug and Castello disclose the incompatibility of *primary* amines salts and lactose. However, Blaug and Castello neither disclose nor suggest that *secondary* amines, much less the particular secondary amine norastemizole, would also be incompatible with lactose. In fact, other references actually teach away from the incompatibility of secondary amines and lactose. For example, Hartaure and coworkers disclose that the secondary amine theophylline does not react with lactose, while the primary amine ethylene diamine does react with lactose. (*See* Specification, pages 3-4, discussing Hartaure *et al.*, *Drug Dev. and Indust. Pharm.*, 17(4):617-630 (1991)). Blaug and Castello neither disclose nor suggest a lactose-free pharmaceutical composition comprising a secondary amine, much less norastemizole. Accordingly, Woosley, Blaug and Castello, either individually or in combination, do not render claim 1, as amended, obvious. For the above reasons, Applicants respectfully request that the rejection of claim 1 be reconsidered and withdrawn.

The Rejection of Claims 9-13, 22-24, 29-32, and 37-40 Under 35 U.S.C. § 103a)

Claims 9-13, 22-24, 29-32, and 37-40 were rejected under 35 U.S.C § 103(a) as being obvious over Woosley in view of The Science and Practice of Pharmacy, 19th ed., vol 2, pp. 1615-1619 (1995) ("Remington's") for the reasons set forth on pages 4-5 of the Office Action. Applicants respectfully traverse.

Remington's discloses solid dosage forms and various ingredients used in solid dosage forms. The Examiner cites Remington's for disclosing microcrystalline cellulose and croscarmellose sodium and alleges that it would have been obviuos to use these excipients in the formulations disclosed in Woosley.

Each of claims 9-13, 22-24, 29-32, and 37-40 requires that the claimed norastemizole pharmaceutical compositions are free of lactose and in the form of a tablet. As discussed above, Woosley does not disclose or suggest a lactose free norastemizole composition in the form of a tablet or even recognize the incompatibility of norastemizole and lactose-based excipients. Remington's does not remedy the deficiencies of Woosley. Remington's, similar to Woosley, does not disclose or suggest a lactose free norastemizole composition in the form of a tablet or recognize the incompatibility of norastemizole and lactose-based excipients. Accordingly, Woosley and Remington's, either individually or in combination, do not render claims 9-13, 22-24, 29-32, and 37-40 obvious. For the above

reasons, Applicants respectfully request that the rejection of claims 9-13, 22-24, 29-32, and 37-40 be reconsidered and withdrawn.

The Rejections of Claims 7, 8, 14-21 and 33-36 Under 35 U.S.C. § 103(a)

Claims 7, 8, 14-21, and 33-36 were rejected under 35 U.S.C. § 103(a) as being obvious over Woosley in view of Remington's and U.S. Patent No. 5,681,582 to Gilis et al. ("Gilis") for the reasons set forth on pages 5-6 of the Office Action. Applicants respectfully traverse the rejection.

Gilis discloses an extended release film coated tablet of astemizole and pseudoephedrine (*See, e.g.*, Gilis, column 1, lines 11-16). The tablet comprises an extended release core comprising pseudoephedrine hydrochloride, a highly viscous hydrophillic polymer as a matrix, and a solid diluent that is covered with an extended release coating (*See, e.g.*, Gilis, column 1, lines 42-51). The resulting covered core is then covered with a coating comprising astemizole, pseudoephedrine hydrochloride, and a hydrophillic polymer and then a seal coating (*See, e.g.*, Gilis, column 1, lines 52-58). The Examiner alleges that Gilis discloses astemizole preparations coated with film forming polymers for extended release and teaches the claimed polymers.

Claims 7, 8, 14-15 depend from independent claims 1 or 9 and include the feature that the pharmaceutical composition further comprises pseudoephedrine. As discussed above, Woosley and Remington's do not disclose or suggest a lactose free norastemizole composition in the form of a tablet or recognize the incompatibility of norastemizole and lactose-based excipients. Gilis does not remedy the deficiency in Woosley and Remington's. The Examiner cites Gilis as teaching the combination of an antihistamine and a decongestant such as pseudoephedrine. The mere disclosure in Gilis that an antihistamine and pseudoephedrine can be combined in a pharmaceutical composition, however, does not remedy the lack of disclosure or suggestion in Woosley and Remington's of a lactose free norastemizole composition in the form of a tablet or the lack of a teaching that norastemizole and lactose-based excipients are incompatible.

Woosley, Remington's, and Gilis, either individually or in combination, also fail to disclose or suggest the compositions recited in claims 16-21. Claims 16-21 are directed to compositions comprising individually coated norastemizole particles. The Examiner acknowledges that Woosley and Remington's fail to disclose or suggest a composition comprising individually coated norastemizole particles. The Examiner, however, alleges that Gilis teaches an astemizole preparation coated with film forming polymers for extended release and then alleges that it would have been obvious to coat the norastemizole of the invention since Woosley teaches that norastemizole and astemizole are both effective in their therapeutic activity.

Giles merely discloses that a core comprising pseudoephedrine hydrochloride, a highly viscous hydrophillic polymer matrix, and a solid diluent can be coated with an extended release coating so that the pseudoephedrine hydrochloride is

released slowly over time. The core coated with an extended release coating is then covered with a composition comprising pseudoephedrine hydrochloride and astemizole that are released immediately. The final composition may then be coated with a seal coating. Gilis merely discloses a coating for a tablet that contains astemizole suspended in a low viscosity polymer (*See, e.g.*, Gilis, column 3, lines 10-17). In contrast, independent claim 16, as amended, recites a solid pharmaceutical composition comprising particles of norastemizole that are *individually* coated with an inert coating. The norastemizole particles are coated before they are admixed with reactive excipients like lactose (*See, e.g.*, Specification, page 17, lines 20-33). By individually coating the norastemizole particles, rather than merely dispersing them in a polymer, allows the resulting particles to be blended with other excipients, including reactive excipients such as lactose, to make a dosage form such as a tablet, capsule and the like (*See, e.g.,* Specification, page 17, lines 18-20 and page 18, lines 10-17). By coating the norastemizole particles, however, the incompatibility between norastemizole and the excipients is avoided. There is absolutely no disclosure or suggestion in Woosley, Remington's or Giles to use norastemizole particles that are *individually* coated before they are admixed with reactive excipients or the unexpected advantages of such compositions. Giles, similar to Woosley and Remington's, does not recognize the incompatibility of norastemizole and excipients such as lactose. Accordingly, Woosley, Remington's, and Gilis, either individually or in combination do not render claims 7, 8, 14-21, and 33-36 obvious. For the above reasons, Applicants respectfully request that the rejection of claims 7, 8, 14-21, and 33-36 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the present application is in condition for allowance and request reconsideration of the application and allowance thereof. If the Examiner has any questions about, or suggested amendments to, the claims, then the Examiner is respectfully invited to call the undersigned to discuss the matter further.

For the above stated reasons, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

No fee is believed to be due for this response. Should any fees be due, however, please charge the required fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: November 26, 2003

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Enclosures